A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation

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Abstract: BACKGROUND AIMS: Glutamine supplementation has been associated with reduced mortality, infections and hospital length of stay in critically ill patients and patients undergoing major surgery. We carried out a meta-analysis to examine randomized clinical trial (RCT)-based evidence of these effects. METHODS: Based on a systematic database search, RCTs published since 1990 were included if they evaluated the effect of parenteral glutamine supplementation against a background of parenteral nutrition. Enteral (tube) feeding in a proportion of patients was allowable. Information on RCT methodology, quality and outcomes was extracted. Random effects meta-analysis followed the DerSimonian-Laird approach. RESULTS: Forty RCTs were eligible for meta-analysis. Parenteral glutamine supplementation was associated with a non-significant 11% reduction in short-term mortality (RR = 0.89; 95% CI, 0.77-1.04). Infections were significantly reduced (RR = 0.83; 95% CI, 0.72-0.95) and length of stay was 2.35 days shorter (95% CI, -3.68 to -1.02) in the glutamine arms. Meta-analysis results were strongly influenced by one recent trial. An element of publication bias could not be excluded. CONCLUSION: Parenteral glutamine supplementation in severely ill patients may reduce infections, length of stay and mortality, but substantial uncertainty remains. Unlike previous meta-analyses, we could not demonstrate a significant reduction in mortality.

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Online Supplement – Additional Results

ICU admission status

			Endpoints available			ICU admission			Inclusion in sensitivity analysis		
Patient group	**Study**	**Ref.**	**Mor.**	**Inf.**	**LOS**	**Yes**	**Partially**	**Unclear**	**Yes**	**No**	**Reason in absence of explicit information**
Surgery	O'Riordain 1994	34		x				x		x	Gastrointestinal surgery
	Morlion 1998	35			x			x		x	Gastrointestinal surgery
	Jacobi 1999	36		x				x		x	Gastrointestinal surgery
	Jiang 1999	37	0	x	x			x		x	Gastrointestinal surgery
	Mertes 2000	56	x		x	x			x		
	Karwowska 2001	52	0	0	x			x	x		Elective aortic aneurysm repair
	Neri 2001	38	0	x	x			x		x	Gastrointestinal surgery
	Spittler 2001	57		x	x	x			x		
	Goeters 2002	29	x		x	x			x		
	Lin 2002	39	0	0				x		x	Gastrointestinal surgery
	Exner 2003	58		0	x	x			x		
	Fuentes-Orozco 2004	59	x	x	x	x			x		
	Klek 2005	40		x	x			x		x	Gastrointestinal surgery
	Yao 2005	41		x	x			x		x	Gastrointestinal surgery
	Jo 2006	42	x	x	x			x		x	Gastrointestinal surgery
	Estivariz 2008	64	x	x		x			x		
	Yeh 2008	43	0	x	x		x			x	
	Asprer 2009	27		x			x			x	
	Engel 2009	67	0	x	x	x			x		Cardiac surgery with cardiopulmonary
	Fan 2009	44		x	x			x		x	Gastrointestinal surgery
	Lu 2011	45		x				x		x	Gastrointestinal surgery
Critical illness	Griffiths 1997/2002	54,55	x	x	x	x			x		
	De Beaux 1998	53	0	x				x	x		Pancreatitis patients, severe
	Wischmeyer 2001	31	x	x	x	x			x		
	Ockenga 2002	32	x	x	x			x		x	Pancreatitis, partially non-severe
	Tjäder 2004	60	x			x			x		
	Xian-Li 2004	61	x	x	x			x	x		Pancreatitis patients, severe
	Zhou 2004	62		x	x			x	x		Burns patients; burn size raging from 30% to 50% of total body surface
	Sahin 2007	33	x		x			x		x	Pancreatitis, partially non-severe
	Cai 2008	28	x		x	x			x		
	Duska 2008	51	x			x			x		
	Fuentes-Orozco 2008	65	x	x	x	x			x		
Mixed	Powell-Tuck 1999	46	x	x	x		x			x	
	Déchelotte 2006	63	x	x	x	x			x		
	Pérez-Barcena 2008	66	x	x	x	x			x		
	Pérez-Barcena 2010	68	x		x	x			x		
	Andrews 2011	10	x	x	x	x			x		
	Cekmen 2011	69	x		x	x			x		
	Grau 2011	70	x	x	x	x			x		
	Wernerman 2011	30	x			x			x		

Table S1: ICU admission status and inclusion in sensitivity analyses where only studies of patients admitted to the ICU were retained. Studies where only a proportion of patients were admitted to the ICU were excluded in these sensitivity analyses. In the absence of explicit information, the criteria described in the main article applied; a brief description is provided in the rightmost column. Ref., Reference number in main article; Mor., Mortality; Inf., Infection; LOS, Length of Stay; ICU, Intensive Care Unit.

Impact on Infectious Morbidity

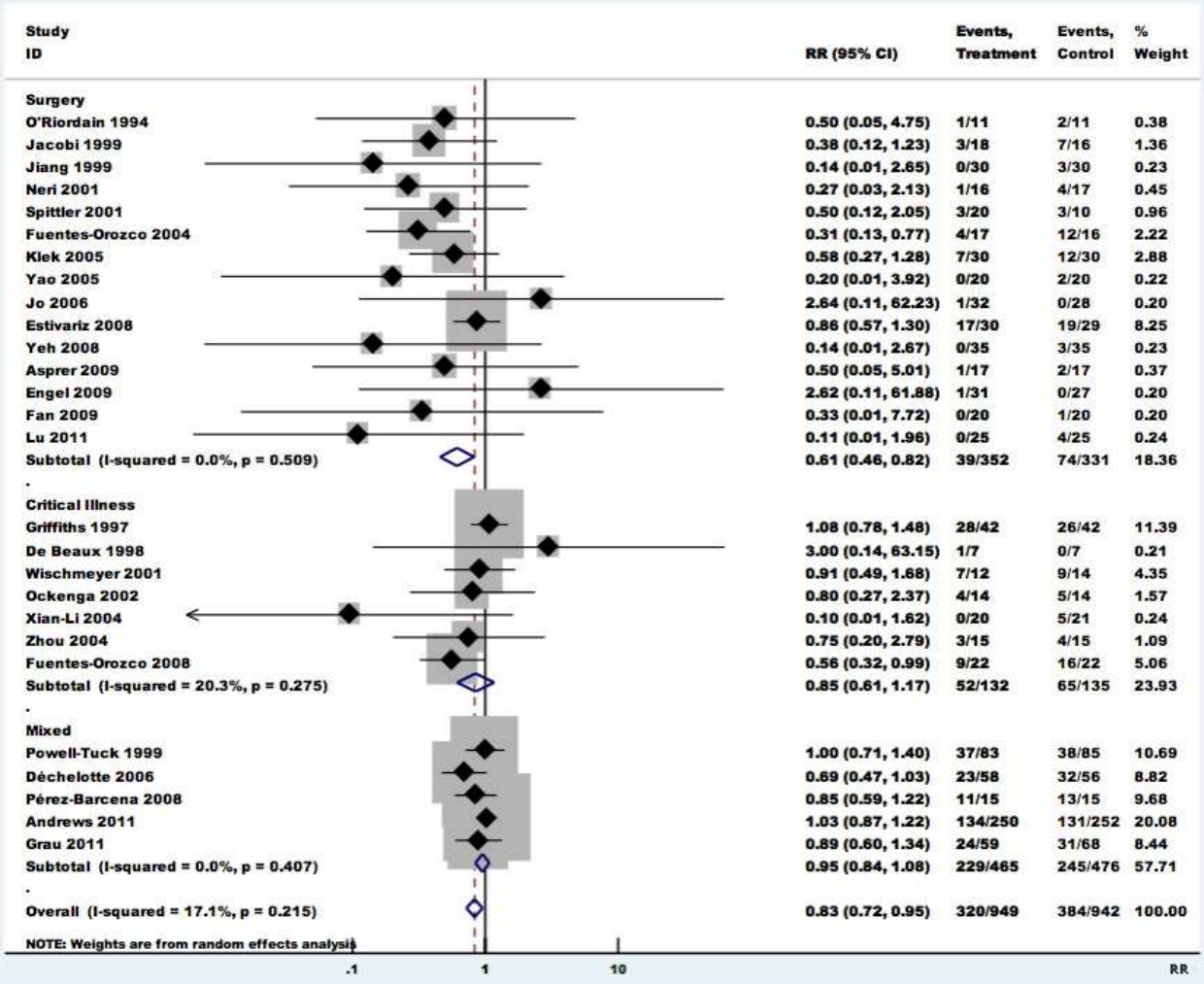

Figure S1: Forest plot of effect of glutamine supplementation on infections.

Subgroup Analyses 1

Subgroup Analysis	MORTALITY			INFECTIONS			LOS		
	Number of Trials [n]	Number of Patients [N]	Effect on Mortality [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on Infections [RR (95% CI), p]	Number of Trials [n]	Number of Patients [N]	Effect on LOS [WMD (95% CI), p]
Glutamine Dosage									
Low Dose (≤0.20 g/kg BW/day)	**6**	**788**	**1.05 (0.87 - 1.27), p=0.615**	**8**	**789**	**1.00 (0.85 - 1.18), p=0.971**	**10**	**969**	**-2.20 (-4.89 - 0.50), p=0.111**
Surgical	2	128	0.74 (0.33 - 1.63), p=0.448	6	259	0.42 (0.15 - 1.18), p=0.099	7	329	-3.42 (-4.97 - -1.88), p=0.000
Critically ill	3	158	0.88 (0.52 - 1.46), p=0.610	1	28	0.80 (0.27 – 2.37), p=0.687	2	138	-2.94 (-6.26 - 0.38), p=0.082
Mixed	1	502	1.11 (0.90 - 1.38), p=0.326	1	502	1.03 (0.87 – 1.22), p=0.717	1	502	4.30 (3.16 - 5.44), p=0.000
High Dose (>0.20 g/kg BW/day)	**16**	**1338**	**0.69 (0.54 - 0.88), p=0.003**	**19**	**1102**	**0.79 (0.67 - 0.93), p=0.006**	**20**	**1140**	**-2.29 (-3.65 - -0.94), p=0.001**
Surgical	3	133	0.44 (0.14 - 1.41), p=0.166	9	424	0.54 (0.35 - 0.83), p=0.006	8	363	-2.43 (-4.10 - -0.75), p=0.004
Critically ill	6	280	0.64 (0.45 - 0.92), p=0.017	6	239	0.83 (0.56 - 1.22), p=0.345	6	265	-1.23 (-2.90 - 0.44), p=0.150
Mixed	7	925	0.76 (0.54 - 1.08), p=0.126	4	439	0.86 (0.71 - 1.04), p=0.111	6	512	-4.77 (-10.69 - 1.16), p=0.115
Duration of Administration									
Short Duration (≤9 days)	**12**	**1649**	**0.96 (0.81 - 1.13), p=0.600**	**20**	**1626**	**0.93 (0.83 - 1.04), p=0.203**	**19**	**1625**	**-2.10 (-3.87 - -0.33), p=0.020**
Surgical	2	97	1.46 (0.19 - 11.34), p=0.719	12	561	0.45 (0.27 - 0.76), p=0.003	11	531	-2.79 (-4.21 - -1.36), p=0.000
Critically ill	3	155	0.71 (0.48 - 1.05), p=0.086	3	124	1.05 (0.79 - 1.39), p=0.744	2	110	0.00 (-1.68 - 1.67), p=0.997
Mixed	7	1397	1.02 (0.85 - 1.23), p=0.836	5	941	0.95 (0.84 - 1.08), p=0.429	6	984	-1.83 (-7.14 - 3.48), p=0.499
Long Duration (>9 days)	**10**	**477**	**0.65 (0.45 - 0.93), p=0.019**	**6**	**235**	**0.62 (0.42 - 0.93), p=0.020**	**10**	**454**	**-2.37 (-3.36- -1.39), p=0.000**
Surgical	3	164	0.57 (0.28 - 1.13), p=0.108	2	92	0.56 (0.20 - 1.57), p=0.271	3	131	-2.34 (-3.91 - -0.78), p=0.003
Critically ill	6	283	0.67 (0.43 - 1.14), p=0.148	4	143	0.59 (0.37 - 0.94), p=0.026	6	293	-2.33 (-3.77 - -0.90), p=0.001
Mixed	1	30	0.50 (0.15 - 1.64), p=0.252				1	30	-8.20 (-17.05 - 0.65), p=0.069
Time Delay before Start of Treatment									
Short delay (≤48 hours)	**4**	**173**	**0.66 (0.45 - 0.97), p=0.035**	**4**	**168**	**1.00 (0.76 - 1.30), p=0.972**	**6**	**243**	**-3.95 (-7.66 - -0.24), p=0.037**
Surgical				1	30	0.50 (0.12 -2.05), p=0.335	2	75	-6.10 (-9.14 - -3.06), p=0.000
Critically ill	3	143	0.68 (0.45 - 1.03), p=0.067	3	138	1.02 (0.76 - 1.30), p=0.879	3	138	-2.07 (-6.44 - 2.29), p=0.352
Mixed	1	30	0.50 (0.15 - 1.64), p=0.252				1	30	-8.20 (-17.05 - 0.65), p=0.069
Long delay (>48 hours)	**8**	**1238**	**0.97 (0.72 - 1.32), p=0.854**	**5**	**732**	**0.97 (0.85 - 1.11), p=0.678**	**4**	**702**	**-1.78 (-8.62 - 5.07), p=0.611**
Surgical	1	63	0.16 (0.02 - 1.27), p=0.083	1	59	0.87 (0.57 -1.30), p=0.487			
Critically ill	2	60	1.26 (0.31 - 5.23), p=0.744	1	14	3.00 (0.14 - 63.15), p=0.480			
Mixed	5	1115	1.06 (0.87 - 1.29), p=0.574	3	659	0.98 (0.85 - 1.13), p=0.815	4	702	-1.78 (-8.62 - 5.07), p=0.611

	MORTALITY			INFECTIONS			LOS		
Subgroup Analysis	**Number of Trials [n]**	**Number of Patients [N]**	**Effect on Mortality [RR (95% CI), p]**	**Number of Trials [n]**	**Number of Patients [N]**	**Effect on Infections [RR (95% CI), p]**	**Number of Trials [n]**	**Number of Patients [N]**	**Effect on LOS [WMD (95% CI), p]**
Study Quality									
Low Quality (≤3.5 points[a])	**9**	**457**	**0.79 (0.53 - 1.16), p=0.221**	**14**	**570**	**0.68 (0.50 - 0.93), p=0.015**	**18**	**851**	**-3.42 (-4.68 - -2.17), p=0.000**
Surgical	3	165	0.75 (0.35 - 1.61), p=0.460	10	457	0.48 (0.29 - 0.81), p=0.005	12	559	-3.18 (-4.63 - -1.73), p=0.000
Critically ill	4	219	0.72 (0.44 - 1.16), p=0.176	3	83	0.65 (0.14 - 3.03), p=0.585	4	219	-2.35 (-3.71 - -0.99), p=0.001
Mixed	2	73	1.85 (0.37 - 9.12), p=0.452	1	30	0.85 (0.59 - 1.22), p=0.368	2	73	-14.63 (-20.93 - -8.32), p=0.000
High Quality (>3.5 points[a])	**13**	**1669**	**0.85 (0.69 - 1.04), p=0.117**	**13**	**1321**	**0.87 (0.74 - 1.02), p=0.080**	**12**	**1258**	**-0.44 (-2.69 - 1.80), p=0.700**
Surgical	2	96	0.37 (0.10 - 1.39), p=0.139	5	226	0.49 (0.23 - 1.06), p=0.071	3	133	-1.68 (-3.50 - 0.13), p=0.069
Critically ill	5	219	0.71 (0.49 - 1.03), p=0.072	4	184	0.87 (0.63 - 1.20), p=0.394	4	184	-0.40 (-2.66 - 1.87), p=0.731
Mixed	6	1354	0.99 (0.82 - 1.19), p=0.932	4	911	0.95 (0.81 - 1.11), p=0.519	5	941	0.25 (-4.69 - 5.18), p=0.923
Disease Severity									
Lower Severity (bg mortality ≤0.20)	**11**	**882**	**0.77 (0.48 - 1.24), p=0.282**	**11**	**542**	**0.69 (0.52 - 0.94), p=0.017**	**12**	**579**	**-3.77 (-5.24 - -2.30), p=0.000**
Surgical		193	0.54 (0.18 - 1.62), p=0.274	6	315	0.48 (0.22 - 1.06), p=0.069	7	323	-3.08 (-4.10 - -2.05), p=0.000
Critically ill	**11**	89	0.64 (0.08 - 5.31), p=0.678	3	83	0.65 (0.14 - 3.03), p=0.585	2	69	-4.32 (-7.39 - -1.25), p=0.006
Mixed	1	600	0.86 (0.49 - 1.50), p=0.592	2	144	0.77 (0.59 - 1.01), p=0.056	3	187	-14.26 (-20.51 - -8.02), p=0.000
Higher Severity (bg mortality >0.20)	6	**1244**	**0.87 (0.72 - 1.04), p=0.126**	**6**	**951**	**0.99 (0.87 - 1.11), p=0.820**	**10**	**1199**	**0.07 (-2.54 - 2.68), p=0.956**
Surgical	4	68	0.67 (0.30 - 1.53), p=0.347				1	68	6.60 (-13.10 - 26.30), p=0.511
Critically ill		349	0.71 (0.53 - 0.96), p=0.028	3	154	0.86 (0.58 - 1.27), p=0.448	5	304	-0.93 (-2.14 - 0.272), p=0.129
Mixed		827	0.94 (0.71 - 1.26), p=0.692	3	797	1.01 (0.88 - 1.16), p=0.915	4	827	0.19 (-4.81 - 5.20), p=0.940

Table S2: Subgroup analyses by patient type. Bg mortality, background mortality risk defined as the risk of death in the control group; BW, body weight; LOS, length of stay; WMD, weighted mean difference; [a] Score points ascribed to the studies in the quality assessment according to a modified Jadad score.

Subgroup Analyses 2

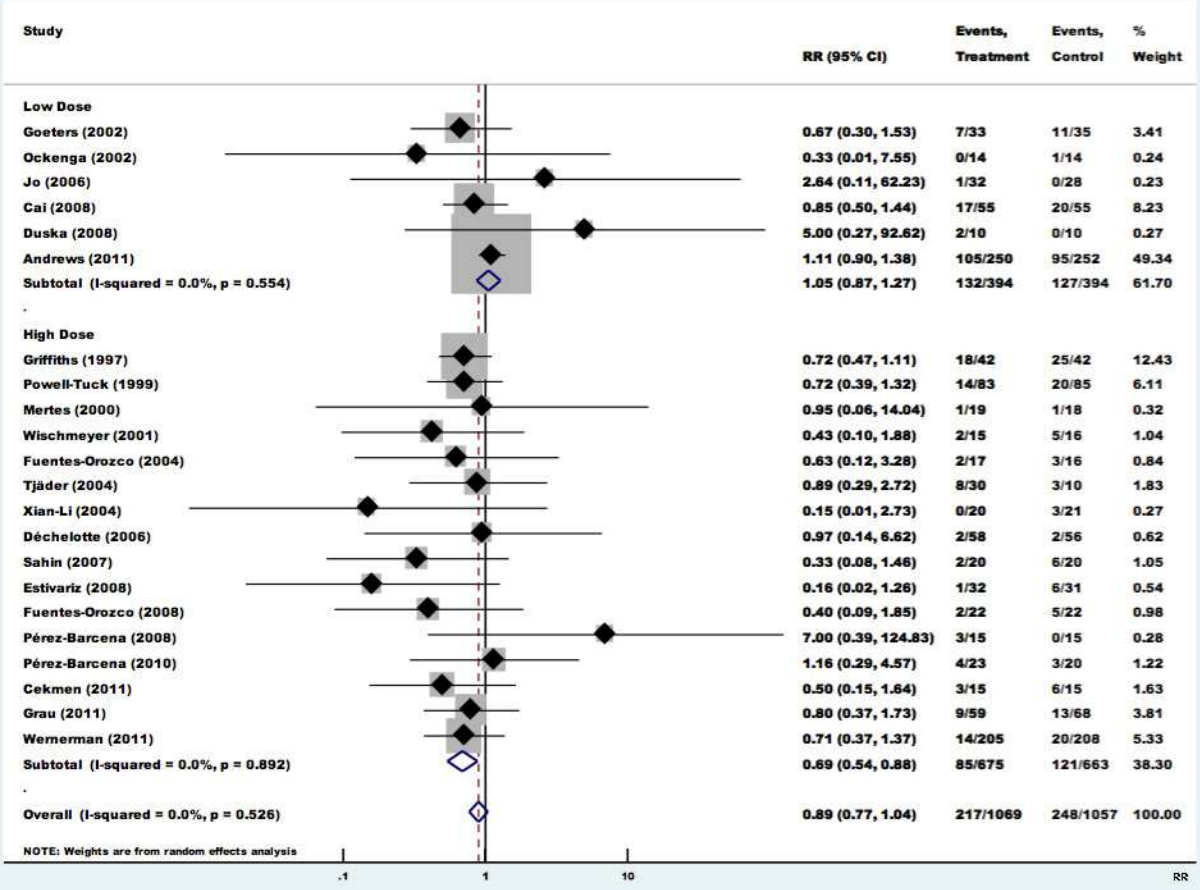

Figure S2: Forest plot of effect of different doses of parenteral glutamine on short-term mortality.

Multivariate meta-regression analysis – short-term mortality

```
Meta-regression                                         Number of obs  =      22
REML estimate of between-study variance                 tau2           =       0
% residual variation due to heterogeneity               I-squared_res  =   0.00%
Proportion of between-study variance explained          Adj R-squared  = 100.00%
Joint test for all covariates                           Model F(2,19)  =    5.79
With Knapp-Hartung modification                         Prob > F       =  0.0109
------------------------------------------------------------------------------
       logrr  |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 High Gln Dose|  -.4480297   .1592667    -2.81   0.011    -.7813788   -.1146807
Long Duration |  -.4324095   .2040148    -2.12   0.047    -.8594173   -.0054017
      Constant|   .1344956    .106165     1.27   0.221    -.0877102    .3567014
------------------------------------------------------------------------------
```

Table S3: Multivariate meta-regression model for RR of short-term mortality. Adj., adjusted; Coef., coefficient; Conf., confidence; High gln dose, glutamine dose >0.20 g/kg body weight/day; I-squared_res, residual I^2; Log RR, logarithm of relative risk; Long admin., duration of administration >9 days; obs, observations; REML, restricted maximum likelihood; Std. Err., standard error; t, t statistic. NOTE: N influenced by availability of covariate information.

Multivariate meta-regression analysis – hospital length of stay

```
Meta-regression                                         Number of obs  =      22
REML estimate of between-study variance                 tau2           =   4.053
% residual variation due to heterogeneity               I-squared_res  =  60.22%
Proportion of between-study variance explained          Adj R-squared  =  62.70%
Joint test for all covariates                           Model F(3,18)  =    5.86
With Knapp-Hartung modification                         Prob > F       =  0.0056
------------------------------------------------------------------------------
         MDLOS  |      Coef.   Std. Err.      t    P>|t|    [95% Conf. Interval]
----------------+-------------------------------------------------------------
    High Gln Dose|  -3.216805   1.412193    -2.28   0.035    -6.183713   -.2498967
     High Quality|   3.691031   1.607237     2.30   0.034     .3143526    7.06771
High Disease Sev.|   2.763086   1.467469     1.88   0.076    -.3199523    5.846125
         Constant|  -3.114436   1.075951    -2.89   0.010    -5.374924   -.8539469
------------------------------------------------------------------------------
```

Table S4: Multivariate meta-regression model for weighted mean difference of hospital length of stay. Adj., adjusted; Coef., coefficient; Conf., confidence; High gln dose, glutamine dose >0.20 g/kg body weight/day; High qual. study, high quality study (see legend to Table S1); I-squared_res, residual I^2; obs, observations; REML, restricted maximum likelihood; Sev. disease, higher disease severity (background mortality >0.20); Std. Err., standard error; t, t statistic; WMD, weighted mean difference. NOTE: N influenced by availability of covariate information.

Risk of Bias Across Studies

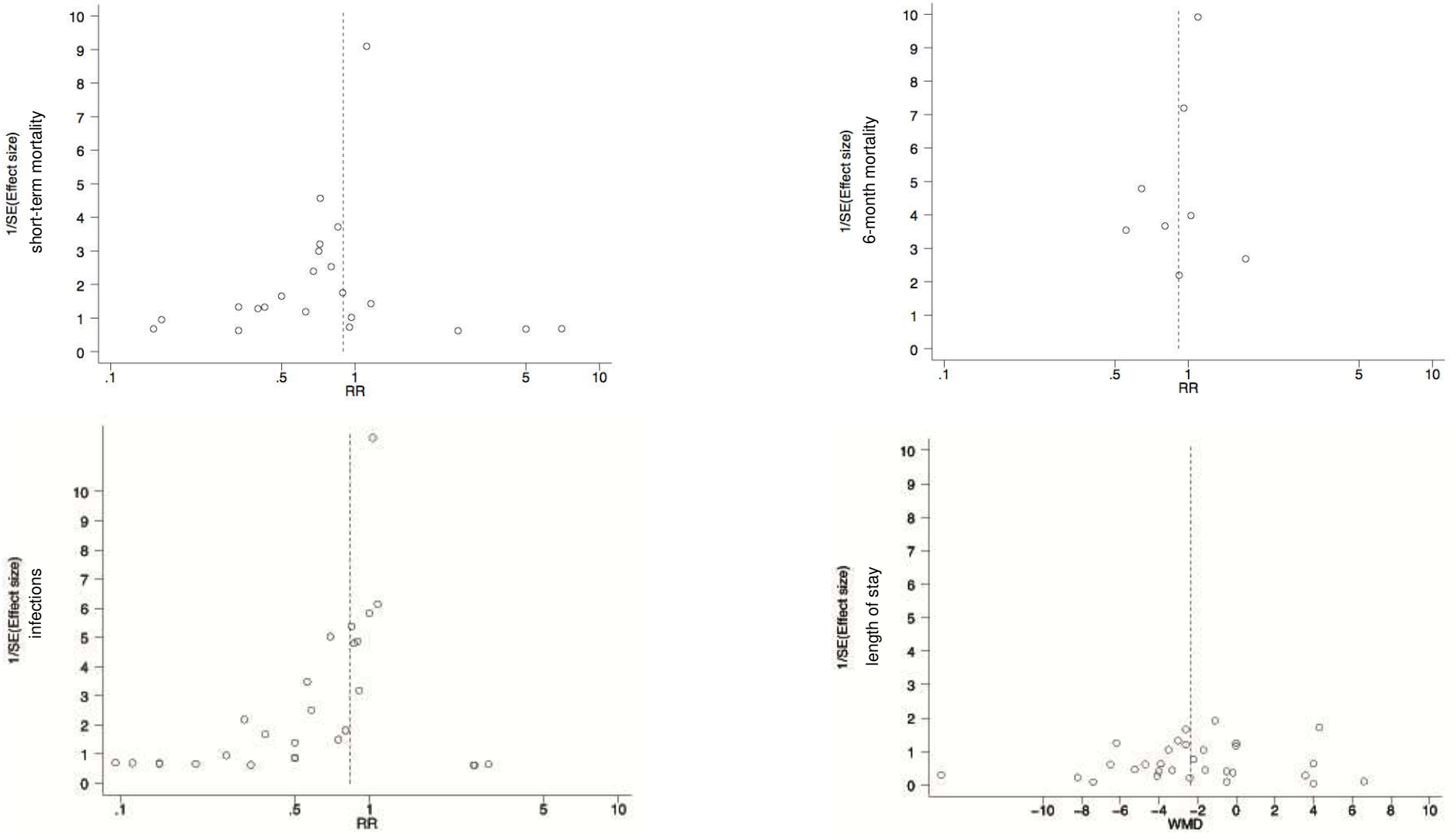

Figure S3: Funnel plots of short-term mortality, 6-month mortality, infectious complications and LOS. SE, standard error; WMD, weighted mean difference.